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Published in:
Child neurology open

DOI:
10.1177/2329048X18779497

Original Article

Child Neurology Open
Volume 5: 1-7

DOI: 10.1177/2329048X18779497
journals.sagepub.com/home/cno
SAGE

Ketogenic Diet in Refractory Childhood Epilepsy: Starting With a Liquid Formulation in an Outpatient Setting

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Abstract

Background: Ketogenic diet in children with epilepsy has a considerable impact on daily life and is usually adopted for at least 3 months. Our aim was to evaluate whether the introduction of an all-liquid ketogenic diet in an outpatient setting is feasible, and if an earlier assessment of its efficacy can be achieved. **Methods:** The authors conducted a prospective, observational study in a consecutive group of children with refractory epilepsy aged 2 to 14 years indicated for ketogenic diet. Ketogenic diet was started as an all-liquid formulation of the classical ketogenic diet, KetoCal 4:1 LQ, taken orally or by tube. After 6 weeks, the liquid diet was converted into solid meals. The primary outcome parameter was time-to-response (>50% seizure reduction). Secondary outcome parameters were time to achieve stable ketosis, the number of children showing a positive response, and the retention rate at 26 weeks. **Results:** Sixteen children were included. Four of them responded well with respect to seizure frequency, the median time-to-response was 14 days (range 7-28 days). The mean time to achieve stable ketosis was 7 days. The retention rate at 26 weeks was 50%. Of the 8 children who started this protocol orally fed, 6 completed it without requiring a nasogastric tube. **Conclusions:** Introduction of ketogenic diet with a liquid formulation can be accomplished in orally fed children without major complications. It allowed for fast and stable ketosis.

Keywords

ketogenic diet, childhood, refractory epilepsy, liquid diet introduction, outpatient setting

Received March 9, 2018. Received revised April 03, 2018. Accepted for publication April 17, 2018.

The ketogenic diet is a high fat, very low-carbohydrate diet. It has become one of the nonpharmacological treatment options for children with medical refractory epilepsy, although its mechanism of action is still unclear.[1] The metabolism of a high amount of dietary fat means that ketone bodies become the main energy source for the whole body and brain. The efficacy of the classical ketogenic diet for children with refractory epilepsy has been strongly supported by 2 randomized controlled trials.[2,3] For children with glucose transporter type 1 deficiency or pyruvate dehydrogenase complex deficiency, ketogenic diet is the treatment of first choice.[4]

The classical ketogenic diet consists of dietary long-chain triglycerides and is based on a ratio of 3:1 or 4:1 (fat:[carbohydrate + protein]). Consequently, the amount of carbohydrate is very restricted and the amount of protein is minimal, which could have a negative influence on physical growth.[5] A ketogenic diet variant with medium-chain triglycerides allows a higher intake of carbohydrates and protein, since medium-chain triglycerides produces more ketones per kilocalorie of energy than long-chain triglycerides. This less restrictive

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medium-chain triglycerides seems as effective as the classical ketogenic diet.[6] However, both the taste of medium-chain triglycerides oil and associated gastrointestinal complaints may compromise the intake.

In clinical practice, the mean time period for adopting the ketogenic diet before considering its continuation/discontinuation because of inefficacy is 3.5 months.[7] A rapid assessment of its efficacy is highly desirable because of the significant impact of the ketogenic diet on the child and his or her caretakers.

Introducing an all-liquid diet requires less complicated instructions than regular and very strict ketogenic diet meals. The implementation of a liquid diet can be much easier for parents or caretakers and ensures a more stable intake with a minimal risk of mistakes. The authors hypothesized that the use of an all-liquid formulation might contribute to an earlier and more stable metabolic situation and level of ketosis, making earlier assessment of efficacy possible. The authors aimed to investigate the feasibility of introducing an all-liquid formulation of ketogenic diet in children with refractory epilepsy and to evaluate whether its efficacy could be assessed reliably within 6 weeks.

Materials and Methods

Patients

This prospective study was carried out in the Beatrix Children's Hospital of the University Medical Center of Groningen, the Netherlands, between 2013 and 2016. All children, aged between 2 and 11 years (oral feeding) or aged between 2 and 14 years (tube feeding), who were referred for ketogenic diet treatment because of refractory epilepsy and who fulfilled predefined inclusion and exclusion criteria according to the Recommendations of the International Ketogenic Diet Study Group[7] could be included. Refractory epilepsy was defined as inadequate seizure control despite treatment with at least 2 antiepileptic drugs in an optimal dose.[8] Treatment with vagus nerve stimulation was not considered as an exclusion criterion.

Ketogenic Diet and Procedures

Ketogenic diet was started in small groups of 2 to 4 children at the same time. After a joint information meeting with the parents and the ketogenic diet team, baseline investigations were performed, including blood and urine tests, electroencephalography, electrocardiography, renal ultrasound, bone mineral density scan, nutritional evaluation, and evaluation of their medication. During this prephase, individual instructions about the ketogenic diet were given to the parents and, if possible, to their child. If there were no contraindications and parents agreed to start with an all-liquid formulation, ketogenic diet was started without an initial fasting period in an outpatient setting. The diet comprised an all-liquid formulation (KetoCal 4:1 LQ) taken orally or by tube with a 10-day, stepwise conversion into a classical liquid ketogenic diet, with a ratio 4:1 of fat:(carbohydrate + protein). A slower introduction was allowed on an individual basis. KetoCal 4:1 LQ could be mixed with carbohydrate-free flavors. All children who could tolerate oral feedings were allowed to have a low-carbohydrate snack, like a piece of cucumber, once or twice a day. Levels of ketosis and glucose were measured in capillary blood samples twice a day (morning and evening) during the first 2 weeks and thereafter once a week and when indicated.

After the introductory phase of 6 weeks, the classical, liquid ketogenic diet was converted into a diet consisting of meals combined with both long-chain triglycerides (KetoCal 4:1 LQ and/or oral dietary products) and medium-chain triglycerides, allowing more protein and carbohydrates to be consumed. The content of the diet was adjusted to calculated percentages of total energy, initially aiming for a distribution of medium-chain triglycerides 43%, long-chain triglycerides 35%, protein 12%, and carbohydrate 10%. Fine-tuning of the diet was based on tolerability, level of ketosis, growth, and individual needs and preferences. During this transition phase, ketosis was measured daily in the evening, until it had again stabilized. Children were seen in the outpatient clinic every 2 weeks during the introductory phase and then regularly until 52 weeks after the start of the all-liquid ketogenic diet.

The study was performed according to the guidelines of the University Medical Center Groningen's medical ethics committee. Since ketogenic diet is part of the regular treatment options for children with pharmacologically resistant epilepsy, the ethics committee did not need to make a formal assessment of this observational study.

Outcomes

Parents and children were asked to keep a diary, including a 4-week baseline period, before the start of the ketogenic diet. The diary included items like seizure type and frequency, use of emergency medication, levels of ketosis and blood glucose, adverse events with special attention for constipation and vomiting, and other individual details when applicable. Changes in antiepileptic drugs during the first 6 weeks were allowed only if they were considered really necessary and these had to be recorded in the diary too.

The primary outcome parameter was time-to-response, defined as time to the first day of a period of at least 7 consecutive days with >50% seizure reduction compared to the seizure frequency before the start of ketogenic diet. Secondary outcome parameters were time to achieve stable ketosis (defined as $\geq$2.5 mmol/L in blood for at least 2 days); the number of children showing a positive response (responder rate) at 6, 12, and 26 weeks; the retention rate at 26 weeks; and the reasons for discontinuation of ketogenic diet.

Results

Patients

Between April 2013 and January 2016, a liquid ketogenic diet was initiated in 16 children. Their clinical characteristics are shown in Table 1. In 10 of 16 children, the seizure frequency was uncountable before the start of ketogenic diet or seizures could not be adequately registered by the parents (difficult to interpret, inconsistent presentation). All children except 1 had multiple seizure types.

Efficacy and Tolerability

Table 2 shows the primary and secondary outcome parameters together with the main aspects concerning tolerability. Only 4 of the 16 children responded well in relation to their seizure frequency, with all of them achieving a response within 4 weeks after the start of the ketogenic diet (Table 2). There were no further responders after 6 weeks. Follow-up time was at least 1 year. The mean time taken to achieve stable ketosis was

Table 1. Demography and Clinical Characteristics.

Patient/ Gender	Age at Onset Epilepsy (years; months)	Age at KD Initiation (years; months)	Number of AEDs[a]	Main Seizure Type	Epilepsy Type/Epilepsy Syndrome	Etiology	Seizure Frequency[a] (per month)	Intellectual Impairment
1/M	1; 2	1; 11	3	Epileptic spasms	West syndrome	Unknown	Uncountable[b]	Severe
2/M	0; 1	4; 8	3	Focal motor	Multifocal	Unknown[c]	30	Severe
3/F	0; 3	3; 2	3	Focal motor	Focal	Unknown	30	Moderate
4/F	0; 3	2; 0	3	Epileptic spasms	West syndrome	Lissencephaly (LIS1-mutation)	Uncountable	Severe
5/M	6; 1	11; 7	3	Focal motor	Focal	KCNT1-mutation	50	Moderate
6/M	0; 7	3; 5	4	Atypical absences	Generalized	Angelman syndrome (15q11.2q12 deletion)	Uncountable	Severe
7/F	0; 1	6; 6	2	Generalized tonic-clonic	Multifocal	Unknown	Uncountable	Moderate
8/M	0; 4	7; 1	3	Focal nonmotor	Focal	Structural lesion after intracerebral hemorrhage	12	Moderate
9/M	2; 0	7; 7	4	Generalized tonic	Lennox Gastaut	Microcephaly with simplified gyral pattern and double cortex	Uncountable	Severe
10/M	1; 0	6; 1	1	Generalized tonic-clonic	Multifocal	Unknown	Uncountable	Severe
11/F	0; 0	3; 0	1[d]	Focal motor	Multifocal	Structural lesion after postnatal hypoglycemia	Uncountable	Severe
12/M	7; 9	9; 0	4	Generalized tonic	Multifocal	Post HSV encephalitis anti-NMDA receptor encephalopathy	Uncountable	Severe
13/M	10; 9	14; 11	3	Focal motor	Multifocal	Cri du Chat syndrome (5p deletion and 4q deletion)	65	Severe
14/F	1; 8	2; 5	2	Generalized atonic	Lennox Gastaut	Unknown	Uncountable	Severe
15/M	4; 0	6; 2	0	Focal motor	NA[e]	Glucose transporter type 1 deficiency (SLC2A1-mutation)	<1	Mild
16//F	0; 7	3; 3	4	Generalized tonic-clonic	Lennox Gastaut[f]	Lobar holoprosencephaly	Uncountable	Severe

Abbreviations: AEDs, antiepileptic drugs; EEG, electroencephalography; HSV, herpes simplex virus; KD, ketogenic diet; NA, not applicable; NMDA, N-methyl-D-aspartate.

[a]Number of AEDs and seizures at KD initiation, respectively.

[b]Uncountable = seizure frequency was too high to count or seizures could not be accurately registered (too difficult to interpret, unreliable presentation).

[c]Brother died of Mitochondrial DNA depletion syndrome (mtDNA) depletion syndrome.

[d]Tapering off of 1 of 2 AEDs started before the introduction of KD and was withdrawn 4 weeks after starting KD.

[e]Uncertain whether attacks were of epileptic origin.

[f]Without typical EEG correlation.

7 days (15/16 children). One child never reached the desired level of ketosis (≥2.5 mmol/L). Not only the 4 responders stayed on the diet after the 6-week introductory phase; 8 children did so for at least 26 weeks (ie, the retention rate at 26 weeks was 50%, both in orally fed and tube-fed children). Apart from reduction in seizure frequency, additional reasons for continuing ketogenic diet, as reported by the parents in their diaries, were changes in seizure type (shorter and/or less severe seizures); less need for emergency medication; and improvement of alertness, cognitive functioning (eg, starting to speak words again, walking again), and/or physical well-being (eg, being able to go to school every day).

In the 8 children who stopped ketogenic diet after 6 weeks, the reasons for discontinuing the diet were inefficacy and/or lack of other benefits, which did not outweigh the burden of the diet. There were no changes to their antiepileptic drug regimens during the first 6 weeks.

Generally, the ketogenic diet was well tolerated. Constipation, the most common adverse event, could be easily controlled by laxatives. Two children needed a high enema

Table 2. Efficacy and Tolerability of KD.

Patient	Responder[a]	Time-to-Response (days)	Time to Stable Ketosis (days)	Level of Ketosis[b] (mmol/L)	Duration KD (weeks)	KD at 26 Weeks	KD at 52 Weeks	Constipation	Admission to Hospital (0-6 weeks)
1	Yes	28	8	2.6-4.0	49	Yes	No	No	No
2	No	NA	2	2.1-5.9	14	No	No	Yes	No
3	Yes	15	7	2.2-5.4	>65[c]	Yes	Yes	Yes	No
4	No	NA	7	2.7-4.9	7	No	No	Yes	No
5	No	NA	7	2.7-5.9	97	Yes	Yes	No	No
6	No	NA	13	2.7-5.9	>165[c]	Yes	Yes	No	No
7	No	NA	1	3.5-5.3	11	No	No	Yes	Beforehand
8	Yes	7	6	3.3-4.6	>203[c]	Yes	Yes	Yes	No
9	No	NA	NA	0.7-1.9	17	No	No	Yes	No
10	No	NA	2	2.4-5.3	15	No	No	Yes	Yes
11	No	NA	6	2.4-5.4	19	No	No	No	No
12	No	NA	20	1.1-5.5	41	Yes	No	No	No
13	No	NA	11	2.7-5.5	9	No	No	No	No
14	No	NA	5	2.8-5.2	26	Yes	No	Yes	No
15	Yes	14	5	2.6-5.0	>141[c]	Yes	Yes	No	Yes
16	No	NA	4	1.9-3.6	12	No	No	Yes	No

Abbreviations: KD, ketogenic diet; NA, not applicable.
[a]Response was defined as >50% seizure reduction.
[b]Level of ketosis week 3 to 6: 10-90 percentiles.
[c]Still continuing KD in April 2017.

during the introductory phase. None of the children experienced an increase in vomiting or other gastrointestinal problems. Introducing the ketogenic diet in an outpatient setting was found to be safe; 2 children had 1 or 2 episodes with vomiting, most likely due to high ketosis (maximums of 5.6 and 7.6 mmol/L) combined with hypoglycemia (1.4 and 2.0 mmol/L, respectively) in the first week, for which they were seen in hospital and could easily be controlled with extra carbohydrates. It appeared that in one of these children, the ketogenic diet had been introduced too rapidly by the mother (within 2 days) instead of using the stepwise instructions for the ketogenic diet. One child, who was electively hospitalized before the start of ketogenic diet for social reasons, had unexplained high ketosis (maximum 6.6 mmol/L) in the first week without further symptoms and with normal blood glucose, which could be corrected with extra carbohydrates.

Ketogenic Diet: All-Liquid Introduction and Transition to Meals

Half of the children were already being tube-fed before ketogenic diet was initiated. For these children and their parents initiating ketogenic diet with an all-liquid formulation was relatively simple. The remaining 8 children were also started with a complete liquid ketogenic diet although they were allowed to replace the liquid formula by an equivalent amount of KetoCal 4:1 LQ as a muffin or pancake based on the KetoCal 4:1 powder, if liquid intake only became problematic. This was only done incidentally. In addition, they were also allowed to have a low-carbohydrate chewable snack, such as a piece of cucumber. Two children received a nasogastric tube temporarily during the first weeks of the introductory phase: one child, known with behavioral problems, because of difficult intake of the KetoCal 4:1 LQ, the other because of insufficient dietary intake before initiating the ketogenic diet. The latter received a percutaneous endoscopic gastrostomy (tube) after discontinuation of ketogenic diet. During the introductory phase, all the children maintained a stable bodyweight. After the conversion to solid meals, 5 of the 6 children without a tube continued using KetoCal 4:1 LQ in their diet for at least another 6 weeks, in combination with oral food preparations and medium-chain triglycerides. For the tube-fed children, the ketogenic diet was adapted by adding medium-chain triglycerides and increasing the amount of protein given. The characteristics of the ketogenic diet during the introductory phase (classical ketogenic diet at 4 weeks) and after the transition to meals (variant with medium-chain triglycerides at 12 weeks) for each patient are shown in Table 3. In 2 children who were totally tube-fed, the classical ketogenic diet was not adapted after 6 weeks because of other severe health problems.

Discussion

Our study shows that introduction of ketogenic diet with a liquid formulation in an outpatient setting is feasible and contributes to achieving a rapid and stable ketosis. Only 1 child did not achieve stable ketosis, which was probably due to noncompliance. In all the children who had a >50% decrease of seizure frequency, time-to-response was less than 4 weeks. Our study therefore supports the idea that it is possible to evaluate the efficacy of this type of ketogenic diet within 6 weeks. This is in line with others who have concluded that most children who

Table 3. Dietary Characteristics.

Patient	Tube	Weight at 4 Weeks (kg)	BMI at 4 Weeks (SD)	Protein at 4 Weeks (g/kgbw)	Protein at 12 Weeks (g/kgbw)	Fat at 12 Weeks (g/kgbw)	MCT: Total Fat at 12 Weeks (%)
1	Yes	12.0	−0.13	1.5	1.5	6.3	0[a]
2	Yes	16.4	−1.00	1.5	1.5	6.6	30.3
3	Yes	14.2	+1.13	1.8	2.2	6.0	11.8
4	Yes	13.8	+0.50	1.6	NA	NA	NA
5	No	37.8	−0.35	1.0	1.4	6.1	31.9
6	Yes	16.0	−1.41	1.3	1.9	5.8	0[b]
7	No[c]	18.4	+0.03	1.3	2.1	5.6	47.1
8	No	23.9	−0.19	1.5	1.9	7.2	43.6
9	No	26.5	+0.24	1.1	1.7	6.7	33.0
10	No[c]	21.0	−0.81	1.5	1.8	6.4	26.7
11	No	16.9	−0.03	1.5	1.9	7.0	41.5
12	Yes	26.8	+0.21	1.4	1.4	6.5	0[a]
13	Yes	39.7	−1.21	1.0	NA	NA	NA
14	No	15.5	+1.81	1.4	2	5.4	26.1
15	No	22.2	+0.76	1.5	2.5	5.2	37.9
16	Yes	16.5	+1.71	0.9	1.4	3.9	0[b]

Abbreviations: BMI, body mass index; KD, ketogenic diet; kg, kilogram; kgbw, kilogram bodyweight; MCT, medium-chain triglyceride; NA, not applicable; SD, standard deviation (based on age).
[a]Classical KD.
[b]Very low energy intake.
[c]Patients 7 and 10 needed a tube during the introduction phase.

show a positive effect on ketogenic diet have a seizure reduction within the first 2 weeks and that it is reasonable to discontinue the ketogenic diet if it did not result in a seizure reduction after 8 weeks.[9] Although individual choices exist, most parents are counselled to continue the ketogenic diet, even if apparently ineffective, for at least 3 months as recommended by the International Ketogenic Diet Study Group.[7] More studies are needed to support that efficacy of the ketogenic diet with solid foods can be evaluated within 6 weeks.

Introducing the ketogenic diet with this all-liquid formulation, KetoCal 4:1 LQ, was simple, minimizing potential dietary errors and with a mean time period of less than 7 days to achieve stable ketosis. In particular, for children who were already tube-fed and for those in an intensive care setting, a liquid diet can be beneficial.[10,11] Also for children who are reluctant to eat ketogenic diet, a liquid ketogenic diet using a formula-based powder is a good alternative.[12] In general, it was well accepted by parents and children. None of the parents or children decided to discontinue or change the diet because of the all-liquid formulation. The intention was to start and stay all-liquid for 6 weeks, but incidentally children were allowed to eat a muffin or pancake based on the Ketocal 4:1 powder, instead of the equivalent amount of KetoCal 4:1 LQ. This happened only sporadically and the risk for dietary errors by allowing this muffin was negligibly small. The level of ketosis in these children remained stable. During the transition to ketogenic meals after 6 weeks, the ketosis in the children became less stable and it took some time to personalize the diet with medium-chain triglycerides and reach stable ketosis again. This did not cause an increase of seizure frequency or a decrease in well-being during this period.

An all-liquid, ready-to-use ketogenic diet formulation including medium-chain triglycerides is not yet available commercially. This makes the transition from the all-liquid phase to solid meals more complicated if a diet with medium-chain triglycerides and more protein is preferred. In total, the dietician's time investment was about the same as that for children who immediately started treatment with a variant of the ketogenic diet with meals, but the transition for children and parents/caretakers was split into easier to manage steps: first adjusting to following a strict diet and monitoring blood values, and later on learning to prepare solid meals with the ingredients permitted.

The responder rate in our study was 25%. This included 1 child with a glucose transporter type 1 deficiency, which is generally known to respond well to ketogenic diet. Our responder rate is lower than the response rate of 38% to 50% reported in 2 randomized control trials.[2,3] The most likely explanation for this is the severity of the children's epilepsy in our study, which seems obvious when looking at their seizure frequencies. In 10 of 16 children, the seizure frequency could even not be determined because the seizures were uncountable, many of the seizures were too difficult to interpret for parents, or seizures went unnoticed. A limitation of our study was the absence of a control group on regular ketogenic diet for comparing responder rate.

The retention rate at 26 weeks of 50% suggests that also other aspects are considered important in the decision to continue ketogenic diet. Some of those are quite subjective, in particular those regarding the child's well-being, and were not formally tested. Retention rate has been suggested as a more useful outcome parameter than the >50% reduction of seizure

frequency, which is especially true for children with many or even uncountable seizures.[13–15] Retention rate combines efficacy and tolerability, but also perceived improvement in activities of daily living and quality of life. It also reflects the impact of a diet on the patient and family's daily life.

Constipation was the most common adverse event of the ketogenic diet, occurring in 9 of 16 children; it is a well-known complication of the diet. The authors did not observe any other gastrointestinal symptoms such as vomiting and diarrhea.[16] Constipation was mostly solved by adding laxatives. The 2 children who needed enemas during the introductory phase had already dealt with persistent constipation before the ketogenic diet introduction. All parents experienced being able to perform the introduction at home as an advantage of our treatment protocol. More importantly, the introduction at home proved to be safe. Initiating ketogenic diet in an outpatient setting is becoming more common and is also standard care in another ketogenic diet center in the Netherlands.[17]

One of the long-term concerns of the classical ketogenic diet is its negative effect on physical growth due to its limited protein content.[5] The ketogenic diet variant with medium-chain triglycerides has the advantage of allowing a higher amount of protein and carbohydrates compared to the classical ketogenic diet (Table 3). Still, no significant differences in growth were found between the classical and medium-chain triglycerides diet groups after 12 months, despite the significantly higher protein intake in the medium-chain triglycerides diet.[5] In our ketogenic diet with medium-chain triglycerides, we prescribed even more protein than Neal et al[5]—with a mean content of 1.86 g/kg compared to 1.67 g/kg. In our study, the growth rates were within normal limits for the children who were on the ketogenic diet for more than 6 months (n = 8) or more than a year (n = 5), except for 1 child whose growth was stable at 1 standard deviation below his original growth curve.

Conclusion

Our results suggest that introduction of ketogenic diet with a liquid formulation is feasible, with good tolerability and acceptance, and the diet can be safely introduced in an outpatient setting. It can be easily applied in tube-fed children but is also a good alternative for insecure parents or in difficult social situations. The mean time to achieving stable ketosis was within 7 days, with a median time-to-response of 2 weeks. Early stable ketosis and a short time period to response made it possible to assess the ketogenic diet's efficacy within 6 weeks, which is an advantage as well. Although the positive response rate was low (4/16), the parents of another 4 children were satisfied with the diet because it led to less severe seizures or improved well-being, which resulted in a retention rate of 50% after 6 months.

Authors' Note

The sponsor had no part in data collection, analysis, interpretation, and/or writing the report. Ketocal LQ was provided by a commercial company (not Nutricia) and reimbursed by the health care provider.

Acknowledgments

The authors thank Jackie Senior for editing the manuscript.

Author Contributions

AW and MVR contributed to conception, design, acquisition, analysis, and interpretation and drafted the manuscript. PMCC contributed to design and interpretation. TJdK contributed to design, analysis, and interpretation. OFB contributed to conception, design, analysis, and interpretation, and drafted the manuscript. All authors critically revised the manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr van Rijn received honoraria for consultancy Danone Research and Development, lecturing and guideline development (Orphan Europe, Nutricia, SSIF), and Board memberships: European Nutrition Expert Panel (Merck Serono), Advisory Board ELEMENT (Danone-Nutricia).

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This was an investigator initiated study which was financially supported by Nutricia Research. Dr de Koning received a research grant from Metakids Foundation, Ride4Kids Foundation, Metabolic Power Foundation (nonprofit), and a research grant from Actelion (for profit). Prof Brouwer received an unrestricted educational grant and payment for lectures from UCB Pharma.

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Ethical Approval

The study was performed according to the guidelines of the University Medical Center Groningen's medical ethics committee. Since ketogenic diet is part of the regular treatment options for children with pharmacologically resistant epilepsy, the ethics committee did not need to make a formal assessment of this observational study.

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